

Response to Wang et al.

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Letter

We refer readers to the commentary by Altshuler and Hirschhorn (1) for an evaluation of current data on the relationship between sequence variation in MEF2A and coronary artery disease (CAD). In addition, we wish to clarify several points. First, as noted in our paper, we initially sequenced the coding regions and intron-exon boundaries of MEF2A in 300 cases only. Missense changes identified in cases (potential “mutations”) were then screened in 300 controls by selective sequencing. Therefore, including these data in a metaanalysis of MEF2A sequence differences in cases and controls is inappropriate. Nevertheless, we should state that we observed 5 missense changes through our sequencing efforts (1 found only in CAD [S360L], 1 only in non-CAD [P432L], and 3 common to both groups [N263S, P432del, and I481V]). Interestingly, N263S is one of the reported causative “mutations” observed in 2 CAD cases (2), but it is also found in our control cohort (an 80-year-old male lacking clinical CAD), which argues against its role as a causative mutation. Second, Wang et al. state that the definition of controls used in our study is inadequate to support valid inference regarding the effect of the 21-bp deletion in MEF2A on CAD. Clearly, we cannot exclude the possibility that the apparently healthy elderly individuals who served as controls in our study may have had occult [...]

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establish the incidence of the 21-bp *MEF2A* deletion and pointing out the possibility of incomplete penetrance. But without proper phenotyping work and experimental biological assessment, it is a misleading report that unfortunately suggests a negative bias and premature dismissal of an important biologic underpinning of CAD.

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Conflict of interest: The authors have declared that no conflict of interest exists.

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We refer readers to the commentary by Altshuler and Hirschhorn (1) for an evaluation of current data on the relationship between sequence variation in *MEF2A* and coronary artery disease (CAD). In addition, we wish to clarify several points.

First, as noted in our paper, we initially sequenced the coding regions and intron-exon boundaries of *MEF2A* in 300 cases only. Missense changes identified in cases (potential “mutations”) were then screened in 300 controls by selective sequencing. Therefore, including these data in a metaanalysis of *MEF2A* sequence differences in cases and controls is inappropriate. Nevertheless, we should state that we observed 5 missense changes through our sequencing efforts (1 found only in CAD [S360L], 1 only in non-CAD [P432L], and 3 common to both groups [N263S, P432del, and I481V]). Interestingly, N263S is one of the reported causative “mutations” observed in 2 CAD cases (2), but it is also found in our control cohort (an 80-year-old male lacking clinical CAD), which argues against its role as a causative mutation.

Second, Wang et al. state that the definition of controls used in our study is inadequate to support valid inference regarding the effect of the 21-bp deletion in *MEF2A* on CAD. Clearly, we cannot exclude the possibility that the apparently healthy elderly individuals who served as controls in our study may have had occult CAD. However, inspection of the original pedigree (QW1576) in which the deletion was first identified (3) reveals that 9 of the 10 carriers of the deletion had clinically manifest disease before the age of 65. In our study, none

of the 3 individuals aged 65 or older carrying the 21-bp deletion had any symptoms of CAD. Therefore, the 3 independently ascertained elderly individuals in our study do not recapitulate the readily observable clinical phenotype originally ascribed to the deletion. It is worth mentioning that these 3 carriers have each recently undergone exercise stress tests and/or nuclear perfusion scans, all of which were completely normal (Duke treadmill score, low risk; normal rest and stress perfusion images), and therefore there is no justification for further invasive coronary angiography. Echocardiography ruled out right ventricular hypertrophy, an abnormality noted in murine *Mef2a* deficiency, and was not intended to determine the presence or absence of CAD.

Third, the concept of incomplete penetrance is only valid for mutations that are known to cause disease. The 21-bp deletion in *MEF2A* does not meet this criterion for the reasons noted by Altshuler and Hirschhorn. To date there is no evidence that the 21-bp deletion in *MEF2A* is any more strongly associated with CAD than are other completely linked sequence variants within the originally reported interval (3). Therefore, unless additional evidence firmly connects *MEF2A* sequence variation and CAD risk, the identification of apparently healthy 21-bp deletion carriers cannot be ascribed to incomplete penetrance.

Finally, we have no vested interest in *MEF2A*: we do not have grant support or any relationships, fiduciary or otherwise, that are in any way contingent on the outcome of the study. In terms of follow-up

studies, a positive result would clearly have been far more interesting and of greater benefit to our laboratories (and was the original goal of this study). Unfortunately this was not the case, and the existing data currently do not support a significant role for *MEF2A* mutations as a cause of CAD.

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